[ L I T E R A T U R E   R E V I E W ]

# Incorporation of a Barrier Protection Cream in the Management of Chronic Hand Dermatitis
## Focus on Data Supporting an Established Hand Protectant Formulation and Modifications Designed to Assist in Barrier Repair

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## ABSTRACT

A commonly encountered skin disorder in outpatient dermatology practice is hand dermatitis. In a considerable subset of patients, hand dermatitis can be a major source of prolonged distress when a pattern of chronicity develops due to repeated exposure to a variety of potential etiological factors. Most of the etiological factors are exogenous in nature. Hand dermatitis is an equal opportunity disease that affects both genders and occurs in individuals from all ethnic and cultural backgrounds. It is important to note that the term hand dermatitis does not refer to one specific diagnostic entity. Rather, hand dermatitis refers to multiple patterns of clinical disease that can be induced by a variety of exogenous sources. Occupational exposures with inadequate hand protection may be an important cause of epidermal barrier disruption, and in some cases contact allergy may be the primary cause or contribute to chronic hand dermatitis. In certain individuals, endogenous sources, such as atopic skin, cutaneous allergy (eczematous pattern), or skin hypersensitivity (urticarial pattern), may innately create predisposition to the development of hand dermatitis. Hand dermatitis can become a chronic problem that is often difficult to manage effectively. As consistency with hand protection and avoidance of irritant and allergenic contactants are integral to the effective treatment of chronic hand dermatitis, there is a high dependence on consistent patient adherence. Regardless of the etiological factors causing chronic hand dermatitis, lack of consistent hand protection is often a major reason why therapeutic results are suboptimal in some cases as exposure to the causes of the hand dermatitis are not adequately prevented. Regular wearing of protective gloves is not always feasible depending on the occupation, and although topically applied skin barrier protectants may be helpful in some cases, scientific data are generally limited with many products. This article provides an overview of hand dermatitis, reviews data supporting the therapeutic benefit of a specific barrier protection hand cream, and discusses ingredient modifications to the original formulation. The newer formulation does not alter the skin barrier protection components; however, the new ingredients were selected to add barrier repair properties to the original product, which was designed only as a skin barrier protectant. (*J Clin Aesthet Dermatol.* 2014;7(2):40–48.)

Hand dermatitis (HD), which is also synonymously referred to as hand eczema, is a commonly encountered skin disorder in ambulatory dermatology practice that may be induced by a variety of etiological factors.[1,2] Population studies have reported that HD affects approximately 10 percent of women and five percent of men over a duration range of 1 to 3 years.[1] However, certain occupations and exposures, especially

those commonly involved with "wet-work," predispose to a much higher likelihood of both acute and chronic HD.[1–4] HD comprises more than 90 percent of cases of occupational skin disease (OSD), with the one-year prevalence of occupation-associated HD reported to be up to 32 percent.[4,5]

It is important to note that HD is a general term that lumps together many potential clinical presentations and etiologies.[1,2,6] As a result, the clinician is encouraged to take into consideration details related to the patient history and clinical presentation of HD, especially in cases of chronic HD. In most cases, exogenous factors are the predominant cause of HD and include frequent exposure of the hands to a variety of irritants and/or to "wet work" at work or home, without adequate hand protection and/or skin barrier repair; endogenous factors may predispose affected individuals to the development of HD and/or promote its chronicity (i.e., atopic skin, cutaneous allergy).[1–7] One report estimated that approximately two-thirds of atopic individuals who perform wet work as hospital employees develop HD.[8] Chronicity of HD is a common problem with two-thirds of individuals with HD followed over a 15-year period reporting persistence of HD.[9] Loss of productivity and financial burden are also major consequences of HD, with approximately two-thirds of affected individuals reported to seek medical assistance and 21 percent taking sick leave because of HD.[1]

Irritant contact dermatitis (ICD), which is a diagnosis made by clinical assessment, is a common cause of both acute HD and chronic HD.[1,3,4] Exposure of the hands to potent alkalis and acids are more likely to cause an acute and severe case of ICD ("chemical burn"), which does not necessarily predispose to chronic HD.[1] Examples of common irritant exposures associated with chronic HD include frequent hand washing; frequent exposure to detergents, solvents, and cleaning agents; and use of poorly formulated skin cleansing products (i.e., harsh, soaps, scrubs).[1,3,5] Detergents, solvents, and cleaning agents (designed for defatting or degreasing) are the major causes of the gradual development of ICD, which is the clinical pattern frequently noted in patients with chronic HD.[1] Trapping of detergents and cleansers (including soaps) under rings can induce ICD of the hands.[1]

Allergic contact dermatitis (ACD), both immediate and delayed, can cause both acute and chronic HD, and is confirmed by patch testing.[1,2,4–6] In cases of chronic HD, it is difficult to distinguish clinically between ICD and ACD, and both can coexist.[1,10] In one report of patients with HD (N=220), the diagnosis was confirmed with patch testing in 12 percent using the standard series and in five percent using additional allergens, with positive therapeutic outcomes resulting from identification of the allergens.[10] The more common allergens associated with ACD in patients with HD are nickel, ethylenediamine, rubber, preservatives, paraphenylenediamine, and potassium dichromate, although there are several other potential contactants.[1] Occupational food handling may be associated with ICD, ACD, contact urticaria, or protein contact dermatitis.[11] Local skin reactions related to handling of foods may present with immediate or delayed hypersensitivity and also contact urticaria; however,



**Figure 1.** Hyperkeratotic heels

eczematous dermatitis may also occur due to several potential sources of ICD (i.e., frequent hand washing) or ACD (i.e., oleoresins of fruits and vegetables, essential oils of vegetables, color additives, flavoring agents, gums, waxes, spices [capsicum, cinnamon, nutmeg, cloves, vanilla], preservatives, antioxidants [i.e., butylated hydroxyanisole]).[1]

Hyperkeratotic eczema (HE) represents a subtype of chronic HD characterized clinically by confluent hyperkeratosis of the anterior surface of hands (palms, digits) and/or distal and lateral digits with little to no visible cutaneous inflammation. The lack of visible inflammation and acute or subacute eczematous dermatitis correlates with the absence of pruritus in many cases, although fissuring may produce discomfort if deep splits develop, especially within natural creases over the finger joints. Low-grade eczematous inflammation may be present in some cases, which is sometimes associated with pruritus, especially of the palms and fingers. HE can also affect the plantar and lateral surfaces of the feet, with hyperkeratotic heels being a common presentation that almost exclusively affects young women. Pustular lesions are not present in HE, which is an important distinguishing feature from palmoplantar pustulosis (pustular psoriasis of the palms and soles). It is important to exclude dermatophyte infection in cases where HE is suspected clinically, as this would warrant use of a topical and/or oral antifungal therapy. Figure 1 demonstrates a 58-year-old woman with hyperkeratotic heels who responded to treatment with CeraVe® Renewing SA Foot Cream. In addition to the restorative barrier repair provided by the moisturizer components of this multivesicular emulsion formulation, salicylic acid included in this branded foot cream and other SA formulations in this product line provides a desmolytic effect, which promotes single cell desquamation that reduces scaling and hyperkeratosis. Although this case did not involve the hands, the clinical changes noted on the feet in Figure 1 are very similar to those seen in hyperkeratotic hand eczema.
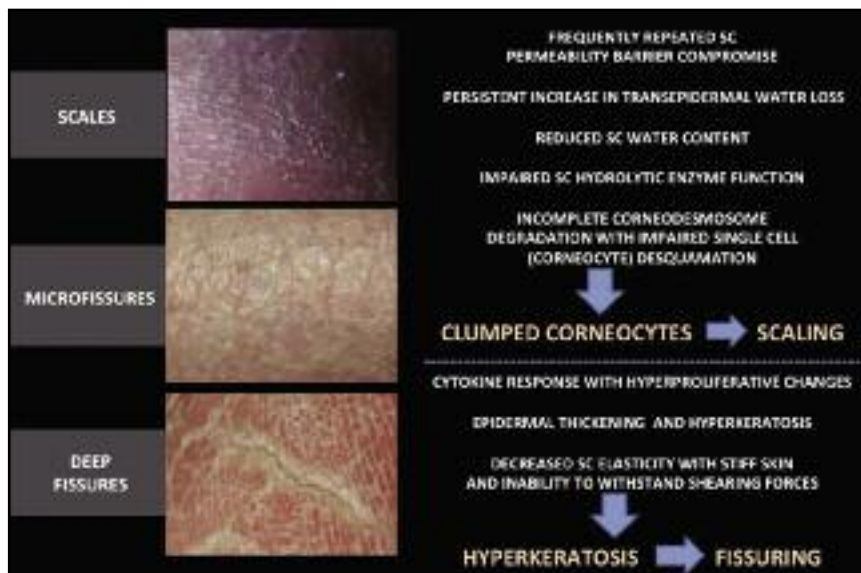
**Figure 2.** Hyperkeratosis and scaling induced by persistent compromise of the stratum corneum (SC)

## CLINICAL PRESENTATIONS OF HAND DERMATITIS

Both acute HD and chronic HD, caused by ICD, ACD, or both, usually present as eczematous dermatitis.[1,2,6,10] Some cases of chronic HD present as hyperkeratotic HD, with absence of visible signs of skin inflammation and mild to absent pruritus. Contact urticaria (CU), an immediate-type reaction that may be more likely to occur in individuals with hand skin already damaged by ICD or ACD from other sources, can occur after contact with several types of foods, especially with various vegetables, seafood, and meats.[1] CU usually presents as diffuse erythema and mild-to-moderate soft edema, with absence of dermatitic skin changes (unless they are pre-existent); stinging and burning alone may occur in those with pre-existing HD.[1,11,12] Although the urticarial-type presentation of CU by definition does not typically fall under a strict umbrella of HD, it may contribute to the overall clinical picture in some patients, especially in those handling foods.[11,12] In some cases, an intensely pruritic vesicular HD develops within minutes after contact with lettuce, endives, or tomatoes in previously damaged or sensitized skin.[1] Nevertheless, the majority of patients with HD exhibit eczematous skin changes that are often associated with pruritis, with chronic HD presenting as subacute eczematous dermatitis, chronic eczematous dermatitis, or hyperkeratotic HD.[1,3,6]

## HAND DERMATITIS, EPIDERMAL BARRIER STRUCTURE AND FUNCTION, AND CLINICAL MANIFESTATIONS

Acute HD that presents as an isolated episode and does not become chronic or frequently recurrent usually presents as an eczematous eruption that is highly responsive to topical corticosteroid (TCS) therapy of adequate potency and proper adjunctive skin care.[1,2] However, chronic HD represents a more difficult management challenge as even during treatment hand skin is often assaulted repeatedly by the factors that induce the HD. This is especially true in occupational cases, in those with regular household responsibilities that require "wet work" and frequent hand washing, in cases of cutaneous allergy where the source of the allergen has not been identified, and when adequate preventative measures are not undertaken consistently.[1,2,4,12] As studies on the physiological properties, anatomic characteristics, and structural and functional properties of the epidermal barrier of hand skin are limited, current information on the epidermal barrier and HD rely on the overall information we have available about the epidermal barrier and responses that occur when the SC permeability barrier is impaired.[4]

Chronic HD appears to represent the progression of cutaneous changes that develop after repeated insults to hand skin continually produce a variety of effects that compromise the SC.[7,13–21] These compromising effects translate to clinical signs of acute and/or chronic HD. Table 1 outlines the response to compromise of SC structure and function and translates the effects of these responses to clinical manifestations of HD. Once the clinical manifestations are fully developed, therapy that includes emphasis on restoring the structural and functional integrity of the SC is vital to the success of reversing the hyperproliferative and eczematous changes that were induced by increased transepidermal water loss (TEWL) and reduced SC hydration.[2,4,7]

The clinical manifestations of prolonged SC permeability barrier impairment include xerosis, scaling, fissuring, hyperkeratosis, and inflammation.[7,13–15] To add, chronic HD can occur in association with endogenous factors, such as atopic skin, and presents clinically over a range of involvement with inflammatory eczema on one end, hyperkeratotic eczema on the other, and mixed patterns that combine both ends of the spectrum in a given patient.[1,7,8] It is important to recognize that the compromise of the SC permeability barrier induced by exogenous etiologies (i.e., harsh cleansers, chemical exposures, low humidity) and compounded in some cases by inherent endogenous factors (i.e., atopic skin) increases TEWL, decreases stratum corneum (SC) hydration, and releases pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6), which set into motion self-reparative responses of inflammation and hyperproliferation.[1,4,7,8,13,20,21] Although these self-repair mechanisms serve initially to counteract the adverse effects of increased TEWL, decreased SC water content (decreased hydration), and disruption of the physiological water gradient, failure to adequately correct the increased TEWL allows inflammation and hyperproliferation to amplify leading to adverse clinical changes.[7,17–21] Hence, the self

| TABLE 1. Compromise of stratum corneum structure and function: correlation with clinical manifestations of hand dermatitis[7,13–21] |
|---|
| Damage to the structure and function of the stratum corneum (SC) causes permeability barrier impairment, which results in increased transepidermal water (TEWL) loss and decreased hydration (SC water content). |
| Decreased epidermal hydration results in suboptimal activity in enzymes, which maintain stratum corneum structure, function, and normal desquamation. |
| Impairment of normal desquamation leads to "clumping of corneocytes," which translates clinically to the production of visible scaling and flaking. |
| Self-repair mechanisms induced by increased TEWL and decreased SC water content include upregulation of certain pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha), which serve to increase epidermal thickness as a means to reduce TEWL. If SC compromise remains unchecked, signal amplification of cytokine release occurs leading to augmented inflammation and hyperkeratotic skin changes. |
| Cutaneous inflammation resulting from persistent SC compromise, irritant contact dermatitis, and/or allergic contact dermatitis produces erythema, edema, and pruritus. |
| Decrease in skin elasticity impairs the ability of skin to respond to shearing forces resulting in microfissuring and macrofissuring, the latter presenting as well-defined deep splits in skin. Reactive epidermal hyperproliferation as a response to increased TEWL and a decrease in epidermal water content leads to hyperkeratosis, increased skin rigidity, and fissuring (Figure 2). |

repair mechanisms can be a "double-edged sword" if there is continued exposure to the exogenous causes of HD and SC damage and the increased TEWL continues to override the epidermal self-repair process.[4,7,8,13,17,20] Persistent increase in TEWL and lower SC water content lead to impaired desquamation, hyperproliferative epidermal thickening and hyperkeratosis, which ultimately reduces skin elasticity and creates "stiff skin." The clinical sequelae of these changes are scaling, hyperkeratosis, and fissuring (Figure 2).

## FACTORS AFFECTING TREATMENT OUTCOMES FOR CHRONIC HAND DERMATITIS

The clinical presentation of chronic HD is dependent on the causative factors, the consistency of efforts to reduce exogenous exposures, and the point in time over the course of the disease. Therapeutic outcomes depend on several obvious factors including the nature of and the types of exposures to exogenous etiological factors, if there are any endogenous predispositions (i.e., atopic skin), and patient adherence with the management program. As consistency with hand protection and avoidance of irritant contactants are vital components of effective treatment of HD, response to therapy is highly dependent on consistent patient adherence.

Importantly, other factors influence outcomes in patients with chronic HD.[1,4,6] In metal workers with HD, risk factors included mechanical forces, atopic skin, and limited time for skin barrier recovery without additional exposure.[22] Topical corticosteroid (TCS) therapy is commonly used and often provides initial visible improvement and symptomatic relief in many cases (especially those presenting with active eczematous dermatitis). However, prolonged TCS therapy is associated with untoward side effects and can impair restoration of SC lipids, thus necessitating periods of corticosteroid-free epidermal barrier repair and use of topical barrier repair therapy concomitantly with TCS treatment.[4,23,24] When utilized appropriately, TCS therapy remains as a very important part of the treatment armamentarium for chronic HD. However, the limitations of TCS use need to be taken into account in chronic HD as persistence and/or frequent episodic flares commonly occur, thus demonstrating the need for strong educational efforts, compliance with preventative measures, and incorporation of an organized multi-dimensional management approach.[1,2,4,6,12]

Regardless of the etiological source(s) of chronic HD, lack of education and hand protection are often major problems that limit the effectiveness of therapies used to treat chronic

HD as the exposure to the causes of the HD are not adequately avoided or diminished.[1,2,4,6] Although use of the proper type of protective gloves is optimal, this approach is not always feasible depending on the occupation of the patient and in some cases causes paradoxical adverse effects.[1,4] Overall, topically applied skin barrier protectants have demonstrated limited benefit, scientific data are generally limited with many commercially available products, many studies evaluate products in laboratory models that do not assess "real-world use," several studies test barrier protection against a limited number of contactants, a considerable number of available studies were published more than 10 years ago using older products, and comparative data are lacking.[1,25,26] This article discusses the differences between barrier protection and barrier repair, reviews data supporting the protectant properties and potential therapeutic benefits of an older barrier protection hand cream (Tetrix®, Coria Laboratories, Ltd., Fort Worth, Texas), and discusses recent ingredient modifications to this original formulation that are incorporated into a new hand cream product (CeraVe Therapeutic Hand Cream®, Valeant Pharmaceuticals, Inc., Bridgewater, New Jersey) that was introduced into the marketplace recently. This newer hand cream product contains the skin protectant formulation identical to the original product without any alteration of the barrier protection components and includes some new ingredients selected to provide the addition of barrier repair properties.

## BARRIER PROTECTION VERSUS BARRIER REPAIR

Repetitive exposure of the hands to eczematous inflammation and prolonged epidermal dessication induced by a persistent increase in TEWL collectively cause several biological and structural changes in the skin.[7] The magnitude and duration of these cutaneous changes in a given patient ultimately translate into the clinical manifestations of chronic HD characterized by varying degrees of inflammation and hyperkeratosis and explain why chronic HD poses several therapeutic challenges. In addition to anti-inflammatory therapies, such as TCS and topical calcineurin inhibitors (TCIs) that are used to control eczematous inflammation, patients are also encouraged to use a gentle cleanser when washing their hands, and to apply a moisturizer at least a few times throughout the day to improve epidermal hydration.[1,2,12] A previous article discussed the formulation characteristics and clinical development of a multivesicular water-in-silicone oil emulsion that incorporated dimethicone and cyclomethicone into a water-impermeable skin barrier protectant cream (Tetrix®).[27] This product was designed to be incorporated into the treatment regimen for chronic HD specifically as an adjunctive skin barrier protectant applied two to three times a day, with data supporting its ability to physically interfere with skin exposure to external irritants and allergens.[27,28] Therefore, it is important for the clinician to have a clear understanding of the differences between a topical cream that is formulated to provide skin barrier protection as compared to one that is formulated with

ingredients selected to provide SC permeability barrier repair.

By definition, a topical formulation that adequately blocks commonly encountered irritants and allergens from gaining access to the skin provides skin barrier protection. This differs mechanistically from a formulation that provides skin barrier repair through the incorporation of ingredients that reduce TEWL, increase SC hydration, replenish physiological lipids, and exhibit properties that appear to support SC function and integrity.[2,15–21] In addition to reduction in TEWL and increase in SC hydration, correction of SC permeability barrier impairment achieved through application of a well-formulated topical barrier repair formulation restores skin elasticity by reducing skin rigidity and SC microfissuring, the latter serving as access points for microbial entry and/or colonization.[7,17] There is some evidence to support that both barrier repair and barrier protection may be of benefit in the management of HD; however, more studies are needed, and improvements in study design and product evaluations are warranted.[1,26,29]

## DATA SUPPORTING THE BARRIER PROTECTION FORMULATION

The original skin barrier protection cream (AMHS-based cream), marketed as Tetrix® Cream, incorporated aluminum magnesium hydroxide stearate (AMHS) and silicate derivatives (dimethicone, cetyl dimethicone, cyclomethicone), formulated as a water-in-oil emulsion. The silicone-based oil-phase outer shell provides a hydrophobic phase, which encases the inner aqueous-phase and water-soluble ingredients, with water comprising approximately two-thirds of the formulation (w/w basis).[27,28] Studies completed during the development of the AMHS-based cream included a comparative 21-day cumulative irritation study, an evaluation of protection against recognized skin allergens and reduced expression of eczematous dermatitis in subjects with known allergic sensitivity, assessment of the resolution of allergic contact dermatitis, an evaluation of reduction in severity of symptoms associated with contact dermatitis, product substantivity testing after handwashing, and a determination of protection against lactic acid stinging.[27,28] The AMHS-based cream has been formulated to provide barrier protection against sensitization and/or irritancy induced by external contactants, which is clinically relevant in the management of HD.

**Cumulative irritation study.**[27,28] The AMHS-based cream was tested as part of a cumulative irritation study evaluating multiple products; Johnson's Baby Oil (Johnson & Johnson) was used as a negative control. Normal healthy adults (N=45 evaluable subjects) were tested under both occlusive and semiocclusive patches applied once daily on the infrascapular region of the upper back. Approximately 24 hours after application, the test patches were removed daily by study staff and evaluated. A 3+ or greater cutaneous reaction at any time point resulted in termination of further patch applications with the observed score assigned and carried forward for the remainder of the study. Cumulative irritation scores were calculated by summing the numerical

irritation grades over the 21 days of testing. Results obtained under semi-occlusion demonstrated a mild rating with the AMHS-based cream, and the results were lower than the negative control. Although it is not suggested that the AMHS-based cream be used under occlusion, occlusive patch-testing results determined that the AMHS-based cream is "probably mild" with clinical use, with a slight potential for very mild cumulative irritation under occlusive patch conditions.

**Skin barrier protection effects.**[27,28] A single-center, investigator-blinded, controlled trial was completed to determine if the AMHS-based cream could provide barrier protection against nickel sulfate, neomycin, and fragrance mixture in adults (N=35 evaluable subjects) with known sensitivity to these allergens (12 allergic to nickel sulfate, 12 allergic to neomycin, 11 allergic to fragrance mixture).

Eligible subjects had four pairs of test sites marked on their upper back. The AMHS-based cream was applied to only one test site in each of the four test-pairs. After the AMHS-based cream dried, the allergen to which the subject was known to be sensitive was applied dispersed in petrolatum to both sites within the first three test pairs. The fourth pair served as a control and included the AMHS-based cream on one side and white petrolatum on the contralateral side. All sites were covered with a Finn Chamber. An open test was also completed in a 16cm$^2$ area on the volar forearm of each subject with the AMHS-based cream applied first followed by the appropriate known allergen for each subject. Signs of delayed-type hypersensitivity were rated according to the North American Contact Dermatitis Group 4-point scale with evaluations completed at 6, 24, 48, and 96 hours after initial application of test materials. Paired patches were occluded for 6, 24, and 48 hours. Statistical analyses were tabulated for collected variables, and differences were analyzed using the paired $t$-test or the Wilcoxon test.

The test outcomes showed that a lower percentage exhibited positive reactions at the test sites where the AMHS-based cream was applied before the allergen as compared to the allergens alone. This observation was noted across all tested subjects. Statistically significant differences between the test sites were present at 24 hours with positivity in 28.6 percent of sites where AMHS-based cream was applied before the known allergen as compared to 57.1 percent with the allergen alone ($p$=0.0039).

Differences between the test sites were also statistically significant at 48 hours with positivity in 68.6 percent of sites where AMHS-based cream was applied before the known allergen as compared to 80.0 percent with the allergen alone ($p$=0.0455). At each time point following all durations of test-site occlusion, the overall proportion of subjects who exhibited positive reactions was lower at the test sites where the AMHS-based cream was applied before the allergen. These results were statistically significant at sites occluded for 24 hours ($p$=0.0039) and 48 hours ($p$=0.0455) and in the latter group at 96 hours ($p$=0.0143). It was concluded that the AMHS-based cream provided skin barrier protection properties against nickel sulfate, neomycin, and fragrance mixture under the usage conditions of this study.

**Resolution of allergic contact dermatitis.**[27,28] An investigator-blinded study was completed in known nickel-sensitive adults (N=10 evaluable subjects) to evaluate if the AMHS-based cream impedes resolution of ACD. ACD was induced at two sites on the volar forearm by occluding nickel sulfate under a Finn Chamber for 48 hours. Reactions were scored for signs of local skin reaction (erythema, induration, edema, flaking, weeping, crusting, ulceration) using a 4-point scale. Crusting or ulceration were not observed in any of the tested subjects after 48 hours of occluded exposure to nickel sulfate.

After removal of the nickel sulfate-impregnated patches at 48 hours and completion of grading of the reactions, the AMHS-based cream was applied to a single site on each subject twice daily for 10 days. Investigator assessments with scoring of the same signs of local skin reaction were completed in all subjects after 4, 7, 9, and 11 days at both the AMHS-based cream treated and untreated sites.

The study results indicated that the AMHS-based cream did not impede the resolution of ACD induced by nickel sulfate, with consistent demonstration of the same or lower severity ratings for the evaluated parameters as compared to the untreated sites. No statistical differences were noted between the scores for both groups. Twice-daily application of the AMHS-based cream showed lower scores for erythema, induration, and edema from Day 4 through Day 11 (end of study), suggesting that the AMHS-based cream may provide some reduction in the signs of ACD as compared to untreated skin.

**Effects in contact dermatitis.**[27,28] An open-label, single-center study evaluated subject assessment of itching and burning in adults with ACD or ICD treated twice daily for 14 days with the AMHS-based cream twice versus nontreated sites. Of the 42 evaluable subjects, 21 were nickel sensitive and 21 presented with HD. A Visual Analog Scale (VAS), ranging from 0 (none) to 100 (worst possible), was used by subjects to rate scores for itching and burning. In the HD study group, subjects had to score associated symptoms of itching and burning with >50 on the VAS scale to enter the study. In the nickel-sensitive study group, exposure to nickel for 48 to 96 hours was used to induce ACD. A minimum of 1+ skin reaction positivity at both forearm sites and grading of itching and burning with >50 on the VAS scale were required for study inclusion. There were no major differences between the groups in VAS scores at baseline. Subjects scored their perceived VAS scores for itching and burning at each of six visits (Visits 2–7) after the baseline visit (Visit 1). Investigator assessment of signs of dermatitis (e.g., erythema, induration, edema) were also recorded as secondary parameters. The study outcomes demonstrated overall that application of the AMHS-based cream decreased itching and burning at all six follow-up visits over the 14-day study based on VAS ratings by study subjects.

HD sites treated with the AMHS-based cream consistently demonstrated lower VAS scores for itching and burning at each follow-up visit through the end of study as compared to the untreated side. The difference became statistically significant ($p$=0.0185) at Visit 3 (Days 4–5) and

continued through Visit 7 (Days 14–15). The VAS scores for itching and burning for HD sites treated with the AMHS-based cream were in the range of 65.8 and 66.2 at baseline, respectively, and at Visit 7, the VAS scores for itching and burning decreased to 25.8 and 22.0, respectively. On the untreated side, the VAS scores for itching and burning at baseline were 67.4 and 68.8, respectively, and decreased at Visit 7 to 48.7 and 48.1, respectively. In subjects with nickel-induced ACD, sites treated with the AMHS-based cream demonstrated faster improvements in itching and burning, although statistically significant differences were not achieved. At Visit 4 and beyond (Days 6–7), the VAS scores for the sides treated with the AMHS-based cream were consistently lower than for the untreated sides. Investigator evaluations indicated that the AMHS-based cream did not impede improvement of the signs of contact dermatitis.

**Substantivity testing.**[27,28] A bilateral, randomized, double-blind study compared the substantivity of AMHS-based cream versus Vaseline Intensive Care® hand cream in adult subjects (N=10) with Fitzpatrick Skin Type I to II. The primary goal of this study was to determine the ability of the test articles to remain on the skin after handwashing, with all study procedures performed on the same day. Prior to application to the hands, the test articles were mixed with a fixed concentration of a pigment-containing cosmetic foundation that does not penetrate skin. The visibility of the pigment on the surface of the skin indicated presence of the test article. Premeasured amounts of the test articles were applied to the hands, with randomization of the sides of application of the test articles to assure proper study blinding. After 15 minutes, a controlled hand wash using a defined routine and designated cleanser was completed by a blinded technician. After completion of washing, the hands were rated for residual presence of pigmentation, and no adverse reactions were noted after application of either test article. The residual pigmentation four-point assessment scale was graded as none (0), minimal (1), mild (2), moderate (3), and significant (4).

The results demonstrated that the AMHS-based cream provides protection against removal by water, including after handwashing. The mean residual pigmentation score for the hands to which the AMHS-based cream was applied was 3.4 compared to 0 for hands that had the Vaseline Intensive Care® hand cream applied. The residual pigmentation scores in the AMHS-based cream group ranged from 2 to 4 as compared to the Vaseline Intensive Care® hand cream group, which were all graded as 0.

**Lactic acid stinging study.**[27,28] Adult female subjects (mean age 39 years) who experienced a stinging sensation when lactic acid 10% solution was applied to their nasolabial folds were evaluated (N=40) to evaluate the ability of the AMHS-based cream to protect against exogenously contacted noxious stimuli and to determine the duration of protection. Subjects rated the severity of stinging response on a four-point scale. In part one of the study, subjects were tested for the degree of protection provided by AMHS-based cream against lactic acid stinging, with three groups of five subjects (n=15) tested at two specified time points after application of the AMHS-based cream. Each subject received two applications of lactic acid 10% solution, randomized as one to each side of the nose (nasolabial fold) at the designated time interval. After application of AMHS-based cream, Group 1 was tested immediately and after 30 minutes, Group 2 was tested at one hour and two hours, and Group 3 was tested at four hours and six hours. After equilibration to room temperature and humidity for 15 minutes, lactic acid 10% solution was applied with the technician applying two strokes with a cotton swab to the test area. Subject assessment of stinging and/or burning was rated at 2.5 minutes after application of lactic acid solution. In the second part of the study, an additional 25 female subjects were tested for lactic acid stinging at four and six hours post-application of AMHS-based cream.

Study outcomes showed that the AMHS-based cream produced a mean decrease in the severity of discomfort (stinging, burning) after application of lactic acid 10% solution. A protective effect against lactic acid stinging/burning appeared to increase over the first few hours after application of the AMHS-based cream, with protection persisting for at least six hours, as this was the last time point measured in this study. In Part 1 of the study, in Group 1, the mean lactic acid stinging/burning score decreased from a prequalification rating of 1.00 to 0.6 immediately after AMHS-based cream application, and at 30 minutes after application, the mean score decreased to 0.2. In Group 2, the mean score decreased from a prequalification rating of 1.00 to 0.6 at one hour after application of AMHS-based cream, and to 0.0 at two hours after application. Also in Group 2, the mean score decreased from a prequalification rating of 1.20 to 0.4 at four hours after application of AMHS-based cream, and to 0.25 at six hours after application of AMHS-based cream. The data from Part 2 of the study evaluates all 30 subjects who underwent lactic acid stinging testing at four hours and six hours after application of the AMHS-based cream, and demonstrated that the mean lactic acid stinging/burning score decreased from a prequalification rating of 1.43 to 0.87 at four hours after application of AMHS-based cream and to 0.83 at six hours after AMHS-based cream application.

**Summary of AMHS-based cream data.**[27,28] The collection of studies completed with the AMHS-based skin barrier protection cream demonstrate several barrier protection properties. Based on the study outcomes, the AHMS-based skin barrier protection cream exhibits minimal irritation potential based on cumulative irritation data, some protection against recognized skin allergens, such as nickel sulfate, neomycin, and fragrance mixture, reduced expression of eczematous dermatitis in subjects with known allergic sensitivity, decreased severity of symptoms associated with contact dermatitis, no impairment of improvement of contact dermatitis, reduction in stinging/burning after exogenous exposure to noxious stimuli based on the lactic acid stinging test, and protection against removal by water during controlled handwashing.

## DEVELOPMENT OF THE NEW MODIFIED THERAPEUTIC HAND CREAM INCORPORATING BARRIER REPAIR INGREDIENTS

As noted above, the newer hand cream formulation (CeraVe® Therapeutic Hand Cream, Valeant Pharmaceuticals, Inc., Bridgewater, New Jersey) contains the same type and concentration of skin barrier protection ingredients and other excipients (i.e., preservatives, water) included in the original AMHS-based cream, and adds additional ingredients incorporated to also provide barrier repair properties. Both the previous and new hand creams are water-in-oil emulsions.[27,30] The three additional barrier repair ingredients are hyaluronic acid, niacinamide, and a registered blend of ceramides and precursor lipids (i.e., ceramide-1, ceramide 6-11, phytosphingosine) (Table 2).[30] The rationale behind incorporating these three barrier repair components is that hyaluronic acid is a potent humectant, niacinamide has been reported to stimulate ceramide and fatty acid production in skin, and ceramides are the predominant physiological lipids comprising the SC lipid bilayer, which physiologically modulates TEWL.[7,13,15,31] Ultimately, a topical product for chronic HD that provides both skin barrier protection and barrier repair would be applicable for use during flares and for long-term daily management. It is recommended that the new therapeutic hand cream formulation be applied as a thin layer to affected areas two to three times per day or as directed by a physician.[30]

With regard to how the new barrier repair ingredients may potentially influence the barrier protection properties of the formulation, both hyaluronic acid and niacinamide are water soluble and would be partitioned into the internal aqueous phase. As a result, it is highly unlikely that they would affect the water-resistant properties of the formulation, which is contributed by the silicate-based outer hydrophobic shell of the emulsion.[27,30] The ceramide blend is itself an aqueous-based emulsion, which will predominantly partition into the aqueous phase.[27] If a small portion of the ceramide blend would partition into the oil phase of the emulsion, the nominal amount would be unlikely to alter the barrier protection properties of the formulation. Importantly, similar to the previous formulation, the new therapeutic hand cream is fragrance-free.[27,30]

## CONCLUSION

Chronic HD is a common dermatological problem that can have a considerably negative impact on quality of life. Multiple etiologies have been identified. Management remains a challenge and requires dedicated compliance with preventative measures and use of therapeutic agents. Epidermal barrier impairment appears to be a critical component in the pathophysiology of chronic HD. As a result, therapeutic measures to protect and repair the SC permeability barrier are suggested as integral parts of management of chronic HD. A recently introduced therapeutic hand cream was formulated based on previously studied barrier protection properties with the addition of ingredients that support barrier repair, suggesting that this product may serve as a valuable addition to the armamentarium for the treatment of chronic HD.

| TABLE 2. Barrier repair ingredients added to original barrier protectant formulation[7,30,31] | |
|---|---|
| **INGREDIENT** | **PROPERTIES THAT IMPROVE BARRIER FUNCTION/STRUCTURAL INTEGRITY OF SKIN** |
| **Hyaluronic acid** | Humectant; high water binding capacity; major component of dermal matrix |
| **Niacinamide** | Potential properties include antioxidant capacity and stimulation of ceramide synthesis and keratinocyte differentiation |
| **Ceramide and precursor lipid blend** | Replenish physiological lipids that comprise the stratum corneum intercellular lipid membrane that are decreased in both lesional (flared) and non-lesional (visibly normal) skin of patients with atopic dermatitis; replenish lipids in other xerotic and eczematous skin conditions and inflammatory dermatoses |

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